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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,838	12/22/2005	Hideki Kubota	281748US0PCT	2991

22850 7590 11/16/2009

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EXAMINER
OH, TAYLOR V

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
11/16/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/561,838	KUBOTA ET AL.	
	Examiner	Art Unit	
	Taylor Victor Oh	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2009*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,7-17 and 21-23* is/are pending in the application.

4a) Of the above claim(s) *21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-17 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/12/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

In view of some additional limitations present in the amendment filed on 7/02/09, there are some issues to be resolved; the examiner has decided to withdraw the previous Office Action and the application is subjected to another Non-final rejection .

The Status of Claims :

Claims 1,3-4,,7-17,21-23 are pending.

Claims 1,3-4,7-17, 23 are rejected.

Claims 21-22 are withdrawn from consideration.

DETAILED ACTION

1. Claims 1,3-4,7-17, 23 are under consideration in this Office Action.

Priority

2. It is noted that this application is a 371 of PCT/JP04/09132 (06/29/2004), which has a foreign documents: Japan 2003-187796(06/30/03) and Japan 2004-099151(06/30/03).

Drawings

3. None.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the claims 15-16, the term " prevention" is recited. However, the specification does not describe how to prevent a disease resulting from abnormal production or secretion of beta-amyloid protein. Also, there are no showings of any evidence for preventing the disease resulting from abnormal production or secretion of beta-amyloid protein at the same time by using the claimed compound. This description is essential to the claimed invention because it allows to distinguish identifying characteristics sufficient show that the applicant was in possession of the claimed invention, and the claim ,as a whole, may not be adequately described where the invention is described solely in terms of a process of its conversion coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its functional language. Furthermore, the contemporary knowledge of the art does not teach " how to prevent " any disease resulting from abnormal production or

secretion of beta-amyloid protein. If we could prevent all the possible permutations and combinations of the disease resulting from abnormal production or secretion of beta-amyloid protein, nobody would be sick from the disease. In addition, more than routine experimentation is involved. See In re Armbruster 185 USPQ 204 (CCPA 1985) and Angstadt et al. , 190 USPQ 152 (CCPA 1990). Therefore, the specification has failed to support enablement for the method for preventing the disease resulting from abnormal production or secretion of beta-amyloid. Therefore, an appropriate correction is required.

Claims 1, 7-9,11-12,14-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for both of R2 and R3 equal to pyridyl having halogens, amine, methanesulfonamide, carbamate, alkyl groups, does not reasonably provide enablement for both of R2 and R3 equal to pyridyl having substituents of the heterocycle, heterocyclic groups, and unsaturated or aromatic monocyclic heterocyclic groups. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims as recited are broader than the scope of enablement. The specification lacks direction or guidance for placing all of the alleged products in the possession of the public without inviting more than routine experimentation

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The specification does not enable any skilled pharmacologist or physician to sue the invention commensurate in scope of these claims.

a) Determining if any particular claimed compounds with both of R2 and R3 equal to pyridyl having substituents of the heterocycle, heterocyclic groups, and unsaturated or aromatic monocyclic heterocyclic groups would require synthesis of the substrate and subjecting them to testing for an inhibitory activity against production or secretion of beta amyloid protein. Considering the large number of compounds to be made, this is a large quantity of experimentation.

b) The direction concerning the claimed compounds is found at page pages 7-26, which merely states that applicants' intent to make and use such compounds.

c) In the instant case none of the working examples contain any formula (1) moieties having both of R2 and R3 equal to pyridyl with substituents of the heterocycle, heterocyclic groups, and unsaturated or aromatic monocyclic heterocyclic groups .

d) The nature of the invention is the treatment of a disease resulting from abnormal production or secretion of beta-amyloid protein with applicants' compounds.

This involves physiological activity. The nature of the invention requires an understanding of the process of forming an amyloid precursor protein (APP) which in turn leads to the formation of beta-amyloid protein; that is, the role of beta-secretase cleaving the N- terminal of beta-amyloid protein and N-APP, a fragment of APP from the peptide's N-terminus, triggering the self–destruct pathway by binding a neuron receptor and the ability of those compounds to inhibit beta-secretase. In view of the unpredictability of the ability of those compounds to inhibit beta-secretase based on the claimed divergent substitutents with varied polarity ,size, and polarizability , the skilled artisan in the art would question the inclusion of such diverse rings, commensurate in scope of these claims. Also, see the MPEP 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

e) There is no reasonable basis for the assumption that the myriad of compounds embraced the present formula(1) will all share the same biological properties. The diverse claimed rings are chemically non-equivalent and there is no basis in the prior art for assuming in the non-predictable art of pharmacology that structurally dissimilar compounds will have such activity ,*In re Surrey* 151 USPQ 724 (compounds actually tested which demonstrated the asserted psychomotor stimulatory and anti-convulsant properties were those having the 3,4-dichlorophenyl substituent at the 2-position on the thiazolidone nucleus not sufficient for enablement of any heterocyclic radical at the same position). *In re Fouche*, 169 USPQ 429 at 434 (a

Markush group including aliphatic and heterocyclic members not enabled for the use of those compounds within the claim having heterocyclic moieties.) *In re Cavallito and Gray*, 127 USPQ 202 (claims covering several hundred thousand possible compounds, of which only thirty are specially identified in appellants' application, not enabled unless all of the thirty specific compounds disclosed had equal hypotensive potency because that fact would strongly indicate that the potency was derived solely from the basic structural formula common to all of them. A wide variation in such potency would suggest that it was due in part to the added substitutents and might be eliminated or even reversed by many of the possible substituents which had not been tried.)

f) The artisan using Applicants' invention to treat diseases with the claimed compounds would be a physician with a MD degree or a pharmacologist with a PhD degree and several years of experience. He or she would be unaware of how to predict *a priori* how changing a heterocyclic ring would affect biological activity.

In view of the divergent rings with varied basicity, steric hinderance, and polarizability, the skilled artisan physician would question the inclusion of such heterocyclic rings, commensurate in scope with these claims.

g) Physiological activity , is well-known to be unpredictable , *In re fisher*, 427 F.2d 833, 839, 166 USPQ 18,24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993): *In re Vaeck*, 947 F.2d 488, 496,20 USPQ2d 1438,1445 (Fed. Cir. 1991).

h) The breadth of the claims includes all of large numbers of compounds of formula(1). Thus, the scope is very broad. The present claims embrace various heterocyclic radicals, which are not art-recognized as equivalent. The specific compounds made are not adequately representative of the compounds embraced by the extensive Markush groups instantly claimed.

MPEP 2164.01(a) states, " A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and /or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1567, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice applicants' invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1,3-4,7-17, 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the phrases " phenyl which may have a substituent " and "pyridyl which may have a substituent " are recited. Each expression of the term " a substitutent " is vague and indefinite because the skilled artisan in the art claim is

unable to figure out or predict what suitable substituents for the claimed compound can be since there are numerous substituents available for the claimed formula compound; the examiner recommends to add the specific substituents for the formula.

In claim 7, the phrase " an aromatic hydrocarbon group " is recited. Each expression of the " aromatic hydrocarbon group" is vague and indefinite because the claim does not elaborate what is meant by the phrase " an aromatic hydrocarbon group "; furthermore, the term "hydrocarbon" may mean that a compound consisting of carbon and hydrogen, but there are numerous hydrocarbons known in the organic chemistry ; there is uncertainty as to what kind of "hydrocarbon" can be applied for the process. Therefore, an appropriate correction is required.

Claim 3 recites the limitation " R^3 " in lines 1-11. There is insufficient antecedent basis for this limitation in the claim.

Claim 4 recites the limitation " R^1 " in lines 1-11. There is insufficient antecedent basis for this limitation in the claim.

Claim 7 recites the limitation " R^2 " in lines 1-88. There is insufficient antecedent basis for this limitation in the claim.

Claim 8 recites the limitation " R^2 " in lines 1-21. There is insufficient antecedent basis for this limitation in the claim.

Claim 9 recites the limitation " R^2 " in lines 1-15. There is insufficient antecedent basis for this limitation in the claim.

Claim 10 recites the limitation " R^2 " in lines 1-21. There is insufficient antecedent basis for this limitation in the claim.

Claim 11 recites the limitation " R^1" in lines 1-21. There is insufficient antecedent basis for this limitation in the claim.

Claim 12 recites the limitation " R^1 " in lines 1-15. There is insufficient antecedent basis for this limitation in the claim.

Claim 13 recites the limitation " R^1 " in lines 1-10. There is insufficient antecedent basis for this limitation in the claim.

In claims 9, 11-12, the phrases " C_{1-6} alkyl-heterocyclic, heterocycle-C_{1-6} alkyl" and " a 5- or 6-membered aliphatic heterocycle " are recited. Each expression of the phrases: "heterocyclic " , " heterocycle" is vague and indefinite because the claim does not elaborate what is meant by each term ; there is no definitive carbon atom range for the hydrocarbon and there are no specific heteroatoms for the heterocyclic group. Therefore, an appropriate correction is required.

Claim Rejections - 35 USC § 102

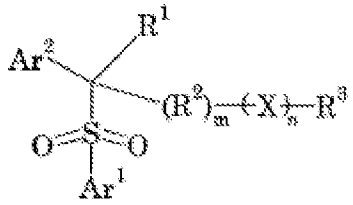
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1,3-4,7,14-17 are rejected under 35 U.S.C. 102(b) as being anticipated clearly by Harrison et al (WO 02/081433).

Harrison et al discloses the following compounds of formula (I) useful for the treatment of Alzheimer disease(see abstract) as shown below (see page 3, lines 1-25 and page 4, lines 1-19) :

The present invention provides a pharmaceutical composition comprising, in a pharmaceutically acceptable carrier, a compound of formula I:



I

wherein:

Ar^1 represents C_{6-10}aryl or heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CN, NO_2, CF_3, OH, C_{1-4}alkoxy or C_{1-4}alkyl which optionally bears a substituent selected from halogen, CN, NO_2, CF_3, OH and C_{1-4}alkoxy;

Ar^2 represents C_{6-10}aryl or heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CN, NO_2, CF_3, OH, C_{1-4}alkoxy or C_{1-4}alkyl which optionally bears a substituent selected from halogen, CN, NO_2, CF_3, OH and C_{1-4}alkoxy;

R^1 represents H, or C_{1-6}alkyl, C_{3-6}cycloalkyl or C_{2-6}alkenyl, any of which is optionally substituted by halogen, CN, NO_2, CF_3, OH, C_{1-4}alkoxy or C_{1-4}alkoxycarbonyl;

R^2 represents a saturated or unsaturated hydrocarbon linking group of up to 6 carbon atoms;

X represents –O-, -S-, -SO_2-, -N(R^5)-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)N(R^5)-, -N(R^5)C(O)-, -OC(O)O-, -N(R^5)C(O)O-, -OC(O)N(R^5)-, -SO_2N(R^5)- or -N(R^5)SO_2-;

R^3 represents C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-4}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl, any of which may be substituted by halogen, CN, NO_2, CF_3, Ar, heterocyclyl, OR^4, $N(R^5)_2$, COR^5, CO_2R^4, $OCOR^5$, or $CON(R^5)_2$; or R^3 represents Ar or heterocyclyl;

R^4 represents H, C_{1-4}alkyl or Ar, or two R^4 groups together with a nitrogen atom to which they are mutually attached may complete an N-heterocyclyl group;

Ar represents phenyl or heteroaryl bearing 0-3 substituents selected from halogen, C_{1-4}alkyl, CN, NO_2, CF_3, OH, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, carbamoyl, C_{1-4}alkylcarbamoyl and di(C_{1-4}alkyl)carbamoyl;

m and n are each 0 or 1, provided that m = 0 if n = 0;

"heterocyclyl" at every occurrence thereof means a cyclic or polycyclic system of up to 10 ring atoms selected from C, N, O and S, wherein none of the constituent rings is aromatic and wherein at least one ring atom is other than C, bearing 0-3 substituents selected from =O, =S, halogen, C_{1-4}alkyl, CN, NO_2, CF_3, OH, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, carbamoyl, Ar and COAr; and

"heteroaryl" at every occurrence thereof means a cyclic or polycyclic system of up to 10 ring atoms selected from C, N, O and S, wherein at least one of the constituent rings is aromatic and wherein at least one ring atom of said aromatic ring is other than C;

or a pharmaceutically acceptable salt thereof.

The expression "heteroaryl" as used herein means a cyclic or polycyclic system of up to 10 ring atoms selected from C, N, O and S, wherein at least one of the constituent rings is aromatic and wherein at least one ring atom is other than carbon. Preferably not more than 3 ring atoms are other than carbon. Where a heteroaryl ring comprises two or more atoms which are not carbon, not more than one of said atoms may be other than nitrogen. Examples of heteroaryl groups include pyridinyl,

(see page 5 ,lines 25-31).

This is identical with the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taylor Victor Oh whose telephone number is 571-272-0689. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Taylor Victor Oh, MSD,LAC
Primary Examiner
Art Unit: 1625

/Taylor Victor Oh/

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11/08/09